UNITED STATES DISTRICT COURT
EASTERN DISTRICT OF MISSOURI
EASTERN DIVISION

IN RE NUVARING® PRODUCTS LIABILITY LITIGATION	)	Case No. 4:08-MD-1964 RWS
	)	ALL CASES

MEMORANDUM AND ORDER

Plaintiffs have filed a motion to exclude the testimony of David A. Grimes, M.D. Defendants ("Organon") have identified Dr. Grimes as an expert witness in this multi-district litigation ("MDL"). Dr. Grimes offers a number of opinions, including 1) neither SHBG nor activated protein C resistance ("APCr") has been validated as a surrogate end point for the risk of venous thromboembolism ("VTE"); and 2) progestins are not associated with an increased risk of VTE; rather, estrogen is the dominant biological mechanism by which VTE occurs from contraceptive use. Plaintiffs ask me to find as a matter of law that Dr. Grimes is unqualified as an expert and that his opinions are so unreliable that they should be excluded from being tested by any cross-examination at trial, being weighed by any jury, or even limited in any respect by any trial judge. For the reasons that follow, Plaintiffs' motion will be denied.

I. BACKGROUND

This MDL relates to the manufacture, marketing, and sale of the prescription pharmaceutical known as NuvaRing. NuvaRing, which is manufactured, marketed, and sold by Organon, is a member of a class of prescription drugs known as combined hormonal contraceptives ("CHCs"). Unlike oral CHCs, NuvaRing takes the form of a flexible ring which releases hormones over the course of treatment. The ring is vaginally inserted by women for birth control. Each month, the ring is removed and a new ring is inserted.

CHCs contain an estrogen, typically ethinyl estradiol ("EE"), and a progestin. The "generation" of CHC depends upon the type of progestin. Each "generation" of CHC typically contains the following progestins: first-generation contains norethynodrel; second-generation contains levonorgestrel; and third-generation CHCs contain desogestrel, gestodene, or norgestimate. NuvaRing uses the active metabolite of desogestrel, etonogestrel, and is therefore considered a third-generation progestin.

Plaintiffs claim that etonogestrel has been linked to an undisclosed increased risk of venous thromboembolism, including deep vein thrombosis and pulmonary embolism.[1] Plaintiffs allege they have been injured by the use of NuvaRing and have asserted the following claims: strict products liability for defective manufacturing, defective design, failure to test, and inadequate warnings; breach of express / implied warranties; and negligence. In opposition to these claims, Organon seeks to present expert testimony from Dr. David Grimes.

Dr. Grimes is board-certified in obstetrics/gynecology and preventative medicine, the latter of which includes epidemiology and biostatistics. (Grimes Declaration, Doc. 1370, Exh. 2, hereinafter "Decl.," at ¶ 4). He serves as a Clinical Professor in the Department of Obstetrics and Gynecology at the University of North Carolina School of Medicine. (Decl. ¶ 4). He was trained in epidemiology, the study of diseases, at the U.S. Centers for Disease Control and Prevention, where he worked for a number of years. (Decl. ¶ 6). While in medical school, Dr. Grimes worked as a blood bank technician, which duties included drawing, typing, and screening blood and performing crossmatches before transfusions. (Decl. ¶ 9).

[1] Venous thromboembolism is a blood clot that forms within a vein. Deep vein thrombosis is a blood clot that forms in a vein not externally visible, typically in the veins of the lower extremities. A pulmonary embolism forms when part or all of a blood clot breaks free and lodges in one of the lungs. These conditions have varying severity and can be life threatening.

Dr. Grimes has studied the association between oral contraceptives and a number of conditions, including benign hepatocellular adenomas, ovarian cysts, hepatocellular carcinoma, and cardiovascular disease. (Decl. ¶¶ 7, 8). Dr. Grimes currently serves on the Data Safety Monitoring Board for a cohort study evaluating the relationship between combined oral contraceptives and venous thromboembolism. (Decl. ¶ 12).

Dr. Grimes has published essays on research methods, and these essays have been compiled into a textbook that is used in schools of public health to teach scientific methods. (Decl. ¶ 15).

At trial, Plaintiffs expect to present evidence that: users of combined hormonal contraceptives experience increased APCr; that SHBG is a protein produced in the liver that increases estrogen exposure in a dose-dependent manner; that SHBG is a marker of total estrogenicity; that SHBG positively correlates with APCr; that increased levels of SHBG and APCr indicate higher VTE risk; and that clinical studies on NuvaRing demonstrate an increase in SHBG, while subsequent independent studies on NuvaRing demonstrate an increase in APCr. Plaintiffs also plan to show that epidemiological studies find an increased risk of VTE in users of NuvaRing compared to users of contraceptives containing second-generation progestins. Plaintiffs' experts will be presented to testify that this risk differential is a function of the type of progestin within the hormonal contraceptive. Finally, Plaintiffs intend to show that the epidemiological studies are consistent with laboratory tests on APCr and SHBG.

In his expert report, Dr. Grimes espouses two opinions related to SHBG and APCr as well as the relationship of VTE risk to progestin and estrogen. Plaintiffs challenge both the qualifications of Dr. Grimes and the methodology he employed in reaching these opinions.

II. LEGAL STANDARD

Federal Rule of Evidence 702 and Daubert v. Merrell Dow Pharms., Inc., 509 U.S. 579 (1993), govern the admissibility of expert testimony. The Daubert standard applies to all expert testimony, whether based on scientific competence or other specialized or technical expertise. See Polski v. Quigley Corp., 538 F.3d 836, 838 (8th Cir. 2008). Rule 702 provides:

> If scientific, technical, or other specialized knowledge will assist the trier of fact to understand the evidence or to determine a fact in issue, a witness qualified as an expert by knowledge, skill, experience, training, or education, may testify thereto in the form of an opinion or otherwise, if (1) the testimony is based upon sufficient facts or data, (2) the testimony is the product of reliable principles and methods, and (3) the witness has applied the principles and methods reliably to the facts of the case.

"[I]t is the responsibility of the trial judge to determine whether a particular expert has sufficient specialized knowledge to assist jurors in deciding the specific issues in the case." Wheeling Pittsburgh Steel Corp. v. Beelman River Terminals, Inc., 254 F.3d 706, 715 (8th Cir. 2001). "Once initial expert qualifications and usefulness to the jury are established, however, a district court must continue to perform its gatekeeping role by ensuring that the actual testimony does not exceed the scope of the expert's expertise, which if not done can render expert testimony unreliable . . . ." Id.

"When faced with a proffer of expert scientific testimony, the trial court must make 'a preliminary assessment of whether the reasoning or methodology underlying the testimony is scientifically valid and of whether that reasoning or methodology properly can be applied to the facts in issue.'" Polski, 538 F.3d at 838 (quoting Daubert, 509 U.S. at 592–93). Thus, under Rule 702, the trial judge also acts as a gatekeeper by screening evidence for relevance and reliability. Daubert, 509 U.S. at 589.

The district court applies a three-part test when screening expert testimony under Rule 702:

> First, evidence based on scientific, technical, or other specialized knowledge must be useful to the finder of fact in deciding the ultimate issue of fact. This is the basic rule of relevancy. Second, the proposed witness must be qualified to assist the finder of fact. Third, the proposed evidence must be reliable or trustworthy in an evidentiary sense, so that, if the finder of fact accepts it as true, it provides the assistance the finder of fact requires.

Polski, 538 F.3d at 839 (quoting Lauzon v. Senco Prods., Inc., 270 F.3d 681, 686 (8th Cir. 2001)).

"Rule 702 reflects an attempt to liberalize the rules governing the admission of expert testimony. The rule clearly is one of admissibility rather than exclusion." Lauzon, 270 F.3d at 686 (internal quotations and citations omitted). "The exclusion of an expert's opinion is proper only if it is so fundamentally unsupported that it can offer no assistance to the jury." Wood v. Minn. Mining & Mfg. Co., 112 F.3d 306, 309 (8th Cir. 1997) (internal quotations and citation omitted).

When assessing the reliability of expert testimony, a trial court should consider several factors, including: "(1) whether the concept has been tested, (2) whether the concept has been subject to peer review, (3) what the known rate of error is, and (4) whether the concept is generally accepted by the community." Miller v. Baker Implement Co., 439 F.3d 407, 412 (8th Cir. 2006) (citing Daubert, 509 U.S. at 593–95). There is no requirement that courts rely on each factor, as the gatekeeping inquiry is flexible and must be "tied to the facts" of the particular case. Kumho Tire Co., Ltd. v. Carmichael, 526 U.S. 137, 150 (1999) (quoting Daubert, 509 U.S. at 591).

"[T]he rejection of expert testimony is the exception rather than the rule." Robinson v. GEICO General Ins. Co., 447 F.3d 1096, 1100 (8th Cir. 2006) (citing Fed. R. Evid. 702 advisory

comm. note). "Vigorous cross-examination, presentation of contrary evidence, and careful instruction on the burden of proof are the traditional and appropriate means of attacking shaky but admissible evidence." Daubert, 509 U.S. at 596.

III. ARGUMENT AND ANALYSIS

Dr. Grimes presents two opinions that Plaintiffs challenge. First, Dr. Grimes concludes that neither SHBG nor APCR has been validated as a surrogate end point for the risk of VTE. Second, Dr. Grimes opines that progestins are not associated with an increased risk of VTE in users of combined hormonal contraceptives. Plaintiffs allege that Dr. Grimes is unqualified to offer both opinions and challenge the reliability of Dr. Grimes's conclusions.

A. Neither SHBG nor APCr Has Been Validated as a Surrogate End Point for the Risk of VTE

1. Qualifications

Plaintiffs argue that Dr. Grimes is unqualified to give this opinion because "he is not a hematologist, biochemist, or scientist who has researched blood factors that regulate clotting." Defendants respond that as an epidemiologist, Dr. Grimes has taught for decades on the fallibility of surrogate end points. (Decl. ¶ 16). They further note that Dr. Grimes has co-authored three published papers on the validity of surrogate end points for venous thrombosis in women using hormonal contraceptives. (Decl. ¶ 16–18).

Rule 702 requires that an expert possess knowledge, skill, experience, training or education sufficient to assist the trier of fact. Dr. Grimes has not only published on research methods, but he has also published on the same topic for which his qualifications are being challenged. I find Dr. Grimes qualified to testify regarding the validation of SHBG and APCr as surrogate end points for the risk of VTE.

2. Methodology

Dr. Grimes has published his opinion in the form of commentary in two medical journals, *Obstetrics and Gynecology* and *Contraception*, upon which he serves as an editor. His opinion has also has been published in a third journal with which Dr. Grimes has no affiliation. In his declaration, Dr. Grimes asserted that despite his connection with *Obstetrics and Gynecology* and *Contraception*, both commentaries underwent the same peer review process that others' writings would receive.

Dr. Grimes's opinion that SHBG and APCr have not been validated as surrogate markers derives from a second opinion: the requirements for validating a surrogate end point. According to Dr. Grimes, there are two requirements for validating a surrogate end point. First, the proposed surrogate end point must correlate with the clinical outcome of interest. Second, the surrogate end point must be shown in at least one prospective study to predict the effect of the exposure on the outcome of interest. Dr. Grimes cites nine published sources for these elements. (Decl. ¶ 23). Dr. Grimes concludes that because the second requirement has not been met for either SHBG or APCr, neither qualifies as a valid surrogate end point.

Plaintiffs argue that Dr. Grimes used unreliable methodology in reaching his conclusions regarding SHBG and APCr. Specifically, Plaintiffs argue that Dr. Grimes "cherry picks" data and completely discards "the vast body" of validating literature, including studies performed by Dr. Rosing, the scientist who developed the APCr assay.

Contrary to Plaintiffs' description of the scientific literature, it appears that there is no general consensus as to whether APCr or SHBG has been validated as an independent risk factor for VTE. Although Plaintiffs assert that the European Medicines Agency uses APCr assays, that organization's guidelines on clinical investigation of steroid contraceptives states that no

surrogate endpoints are generally accepted for the risk of VTE. (Doc. 1316, Exh. 11 at ¶ 4.2). It is true that Dr. Grimes finds fault with the studies cited by Plaintiffs. However, an expert's differing opinion, including the reasons for exclusion of data, is a topic best left for cross-examination. See Kuhn v. Wyeth, Inc., 686 F.3d 618, 633 (8th Cir. 2012). Dr. Grimes may testify as to studies and publications involving SHBG and APCr and VTE risk.

B. Progestins Are Not Associated with an Increased Risk of VTE in Users of Combined Hormonal Contraceptives

1. Qualifications

Organon argues that Dr. Grimes's qualifications are based on his "knowledge, experience, and education as an expert in contraception, a reproductive epidemiologist, and an OB-GYN who treats women with VTEs." Plaintiffs argue that Dr. Grimes lacks necessary experience and training in hematology. At his deposition, Dr. Grimes testified that his opinion as to the role progestin plays in hormonal contraceptives derives from epidemiological studies. (Doc. 1316, Exh. 1 at 147–48). Dr. Grimes is qualified to give epidemiological opinions through the experience and knowledge attained during his studies and tenure at the U.S. Centers for Disease Control and Prevention.

2. Methodology

In reaching his opinion, Dr. Grimes relied upon a number of studies concluding that progestin-only contraceptives do not significantly increase risk of VTE. (Decl. ¶ 30). He further relied upon studies that concluded that risk of VTE is a class effect of the estrogen component of oral contraceptives. (Decl. ¶ 30). Finally, Dr. Grimes cited a study that found all hormonal contraceptives have a similar risk of VTE. (Decl. ¶ 31).

Plaintiffs argue that Dr. Grimes used unreliable methods in reaching his conclusions. Plaintiffs note that Dr. Grimes is unable to explain the biological mechanism governing VTEs

and that Dr. Grimes's opinion is contrary to the generally accepted notion that both estrogen and type of progestin influence VTE.

Rule 702 does not require that an expert identify the precise causal mechanism for a given result. See Daubert v. Merrell Dow Pharmaceuticals, Inc., 43 F.3d 1311, 1314 (9th Cir. 1995) ("Causation can be proved even when we don't know precisely how the damage occurred, if there is sufficiently compelling proof that the agent must have caused the damage somehow."). Neither does there appear to be general consensus as to whether both estrogen and progestin influence VTE. Experts for both Plaintiffs and Organon cite numerous publications in favor of their positions on this issue. Instead of attacking Dr. Grimes's methodology, Plaintiffs impeach his conclusions. The time and place for such arguments is at trial through cross-examination and the presentation of Plaintiffs' own evidence. See Bonner v. ISP Technologies, Inc., 259 F.3d 924, 929–30 (8th Cir. 2001). Dr. Grimes has presented sufficiently reliable bases for his opinion for admittance at trial. Plaintiffs will have the opportunity to present their own evidence at that time.

IV. CONCLUSION

For the foregoing reasons, the Court finds Dr. Grimes qualified to opine as to the matters stated in his expert report as explained and clarified in Organon's responses to Plaintiffs' motion. Further, these opinions, as grounded in credible articles, studies, reports, and personal experience, are based on a reliable methodology. Plaintiffs' arguments seeking exclusion of his opinions are relevant to the weight and credibility of the proposed testimony.

Accordingly,

IT IS HEREBY ORDERED that Plaintiff's motion to exclude the testimony of Defendants' expert witness David Grimes **[Doc. 1315]** is **DENIED.**

RODNEY W. SIPPEL
UNITED STATES DISTRICT JUDGE

Dated this 4th day of March, 2013.